REMARKS

Applicants thank the Examiner for examining the present application and preparing the office action dated November 30, 2005. Claims 1-30 are pending in this application, with claims 17 and 24-30 withdrawn from consideration. Claims 18 and 19 were rejected under 35 USC 112, ¶2; claims 1-2, 10-15, 18, and 21-22 were rejected under 35 USC 102(b) over Jones *et al.*, US Patent No. 5767147; claim 19 was rejected under 35 USC 103(a) over Jones *et al.*; and claims 3-9, 20, and 23 were rejected under 35 USC 103(a) over Jones *et al.* in combination with Kauvar *et al.*, US Patent No. 5556942, further in view of the USP Dictionary of USAN and International Drug Names, 2005. These rejections, to the extent they are considered applicable to the amended claims, are respectfully traversed.

The 35 USC 112, ¶2 rejection

Claims 18-19 were rejected under 35 USC 112, ¶2 for indefiniteness for containing a narrow range within a broader range. Claims 18 and 19 have each been amended so that they no longer recite a narrow range within a broader range. Withdrawal of the rejection of claims 18-19 is respectfully requested.

The 35 USC 102(b) rejection

Claims 1-2, 10-15 [the rejection states "10-13, 14-15", which is the same], 18, and 21-22 were rejected under 35 USC 102(b) as being anticipated by Jones *et al.*, US Patent No. 5767147. This rejection is respectfully traversed.

Claim 1 recites "A method of combination cancer therapy in a mammal comprising administering a therapeutically effective amount of a GST-activated anticancer compound and a therapeutically effective amount of another anticancer therapy" (emphasis added). Claims 2, 10-15, 18, and 21-22 are either dependent on claim 1 or also recite the use of a GST-activated anticancer compound.

Applicants submit that Jones *et al.* fails to disclose a GST-activated anticancer compound, as required by claims 1-2, 10-15, 18, and 21-22.

The Office Action states that:

> "Jones et al. teach ... a haloenol lactone derivative .... With regards to the haloenol lactone, the patent teaches (column 5, lines 45-67) that the haloenol lactone derivative contains a glutathione thioether, a glutathione S-oxide, or a glutathione-S-S-dioxide thiol ether. ... Thus, while Jones et al. do not characterize the haloenol lactone derivative as being a 'GST-activated anticancer compound', the claimed functional limitation would be an inherent property of the referenced method since the specification discusses (page 8, paragraph 0034) that a 'GST-activated anticancer compound' is a compound comprising a glutathione. Thus, it does not appear that the claim language or limitation results in a manipulative difference in the method steps when compared to the prior art disclosure."

Applicants do not disagree that Jones *et al.* teach a haloenol lactone. Nor do Applicants disagree that Jones *et al.* teach that the haloenol lactone may contain a glutathione thioether, a glutathione S-oxide, or a glutathione-S-S-dioxide thiol ether.

However, Applicants disagree that Jones *et al.* teach that the haloenol lactone must contain at least one of those three glutathione-related moieties (as implied by the "contains" of the Office Action), since it is clear from column 5, lines 45-67 of Jones *et al.* that the haloenol lactone need not contain any one of them – for example, in Formula I, R^1 and R^2 may together form an epoxy group or a double bond and R^3 can be hydrogen, so that no glutathione-related moiety is present. In fact, the only two haloenol lactones actually described by Jones *et al.* are 3-cinnamyl-(α,β-epoxy)-5(E)-bromomethylidenetetrahydro-2-furanone ("compound 1" – see column 13, lines 52-54) and 3-cinnamyl-5(E)-bromomethylidenetetrahydro-2-furanone ("compound 2" – see column 13, lines 31-32), neither of which contain a glutathione thioether, a glutathione S-oxide, or a glutathione-S-S-dioxide thiol ether. Thus Jones *et al.* do not disclose any glutathione-containing haloenol lactone, merely a Markush group of haloenol lactones of which some members contain glutathione.

While the Office Action admits that "Jones *et al.* do not characterize the haloenol lactone derivative as being a 'GST-activated anticancer compound'", it continues by saying that "the claimed functional limitation would be an inherent property of the referenced method since the specification discusses (page 8, paragraph 0034) that a 'GST-activated anticancer compound' is a

compound comprising a glutathione" (emphasis added). This assertion is incorrect because it ignores the totality of Applicants' definition of a GST-activated anticancer compound: paragraph **[0034]** as a whole states that "A 'GST-activated anticancer compound' is a compound comprising glutathione or a glutathione analog chemically linked to a cytotoxic moiety such that the cytotoxic moiety is released by cleavage from the glutathione or glutathione analog in the presence of one or more GST isoenzymes" (emphasis added).

The generically disclosed haloenol lactones of Jones *et al.* are not GST-activated anticancer compounds because, although they may contain glutathione or a glutathione analog, they do not contain that glutathione or a glutathione analog chemically linked to a cytotoxic moiety such that the cytotoxic moiety is released by cleavage from the glutathione or glutathione analog in the presence of one or more GST isoenzymes. If glutathione is present in the generically disclosed haloenol lactone of Jones *et al.* it is covalently linked to an aryl-propyl/propenyl-(haloenol lactone). Jones *et al.* neither disclose nor suggest that the aryl-propyl/propenyl-(haloenol lactone) moiety is either (a) cytotoxic or (b) released by cleavage from the glutathione in the presence of one or more GST isoenzymes, both of which elements are required by Applicants' definition of a GST-activated anticancer compound. The specifically disclosed haloenol lactones of Jones *et al.* do not contain glutathione, and fail the definition of GST-activated anticancer agent for that reason also.

Applicants do not dispute that the generically disclosed haloenol lactones of Jones *et al.* are stated, and the two actual examples of haloenol lactones are shown, to be inhibitors of GST isoenzymes. However, that does not imply that the haloenol lactones of Jones *et al.* (glutathione-containing or otherwise) are cleaved by a GST isoenzyme, still less that those containing glutathione will release a cytotoxic moiety that was originally chemically linked to the glutathione.

Applicants therefore submit that Jones *et al.* does not anticipate claims 1-2, 10-15, 18, and 21-22 under 35 USC 102(b) because they fail to disclose a GST-activated anticancer compound: the generically disclosed compounds are not disclosed to contain glutathione or a

glutathione analog chemically linked to a cytotoxic moiety such that the cytotoxic moiety is released by cleavage from the glutathione or glutathione analog in the presence of one or more GST isoenzymes; and beyond that the actually disclosed compounds do not contain glutathione.

By not arguing the other aspects of the rejection (e.g. dosing), Applicants do not intend to be considered to agree with the Office Action's expression of those aspects – they are not being argued here because the issue of non-disclosure of a GST-activated anticancer compound by Jones *et al.* is dispositive of the propriety of the rejection.

Withdrawal of the rejection of claims 1-2, 10-15, 18, and 21-22 is respectfully requested.

The 35 USC 103(a) rejections

Claim 19 was rejected under 35 USC 103(a) as being unpatentable over Jones *et al.*. This rejection is respectfully traversed.

The Office Action in effect states that Jones *et al.* contains all elements of claim 19 (for the same reason as the reference is said to anticipate claims 1-2, 10-15, 18, and 21-22 above) except that "Jones et al. does not explicitly teach that dosing is about 500-1000 mg/m^2 at 1-5 week intervals."

For the reasons discussed in the discussion of the rejection of claims 1-2, 10-15, 18, and 21-22 above, Applicants submit that Jones *et al.* does not render claim 19 unpatentable under 35 USC 103(a) because they fail to disclose a GST-activated anticancer compound: the generically disclosed compounds are not disclosed to contain glutathione or a glutathione analog chemically linked to a cytotoxic moiety such that the cytotoxic moiety is released by cleavage from the glutathione or glutathione analog in the presence of one or more GST isoenzymes; and beyond that the actually disclosed compounds do not contain glutathione.

By not arguing the dosing aspect of the rejection, Applicants do not intend to be considered to agree with the Office Action's expression of that aspect – it is not being argued here because the issue of non-disclosure of a GST-activated anticancer compound by Jones *et al.* is dispositive of the propriety of the rejection.

Withdrawal of the rejection of claim 19 is respectfully requested.

Claims 3-9, 20, and 23 were rejected under 35 USC 103(a) as being unpatentable over Jones *et al.* in combination with Kauvar *et al.*, US Patent No. 5556942, further in view of the USP Dictionary of USAN and International Drug Names, 2005 (which includes the entry for canfosfamide hydrochloride). This rejection is respectfully traversed.

The Office Action in effect states that Jones *et al.* contains all elements of claims 3-9, 20, and 23 (for the same reason as the reference is said to anticipate claims 1-2, 10-15, 18, and 21-22 above) except that "Jones et al. does not explicitly teach that the GST-activated anticancer compound is canfosfamide hydrochloride. Nor does Jones et al. teach that the dosing of said canfosfamide hydrochloride is about 500-1000 mg/m^2 at 1, 2, 3, or 4 week intervals."

For the reasons discussed in the discussion of the rejection of claims 1-2, 10-15, 18, and 21-22 above, Jones *et al.* fail to disclose a GST-activated anticancer compound: the generically disclosed compounds are not disclosed to contain glutathione or a glutathione analog chemically linked to a cytotoxic moiety such that the cytotoxic moiety is released by cleavage from the glutathione or glutathione analog in the presence of one or more GST isoenzymes; and beyond that the actually disclosed compounds do not contain glutathione.

Applicants do not dispute that Kauvar *et al.* discloses the class of GST-activated anticancer agents claimed in claims 3-9, 20, and 23, including TER286, and their salts (although canfosfamide hydrochloride is not specifically disclosed); and also do not dispute that the USP Dictionary of USAN and International Drug Names, 2005, entry for canfosfamide hydrochloride discloses canfosfamide hydrochloride and demonstrates that TER286 and canfosfamide are the same. Applicants therefore do not dispute that canfosfamide hydrochloride is a GST-activated anticancer agent within the definition of paragraph **[0034]**.

The Office Action reasons that "it would have been *prima facie* obvious ... to substitute the haloenol lactone compounds as taught by Jones et al. for the GST-activated compound as taught by Kauvar et al. because each of the agents have been individually taught in the prior art to be useful at treating cancer and/or drug resistant tumor cells" (emphasis added).

The rejection, so stated, fails because to substitute the haloenol lactone compounds of Jones *et al.* for the GST-activated compound of Kauvar *et al.* would only result in monotherapy using the haloenol lactone compounds of Jones *et al.*. If that is what is intended by the rejection, the rejection is doubly defective because (a) claims 3-9, 20, and 23 are to combination therapy, and (b) the compounds whose use is claimed in claims 3-9, 20, and 23 are not haloenol lactone compounds, but the compounds disclosed in Kauvar *et al.* and the USP Dictionary of USAN and International Drug Names, 2005.

For a 35 USC 103(a) rejection of claims 3-9, 20, and 23 to be proper with Jones *et al.* as the primary reference, the rejection must be able to state that "it would have been *prima facie* obvious ... to substitute the haloenol lactone compounds as taught by Jones *et al.* with the GST-activated compound as taught by Kauvar *et al.*"; or, in other words, that it would have been obvious to substitute the GST-activated compound as taught by Kauvar *et al.* for the haloenol lactone compounds as taught by Jones *et al.*. Applicants believe that this is the reasoning intended by the rejection, and will therefore respond to it also.

Assuming that the rationale for the rejection is "it would have been *prima facie* obvious ... to substitute the haloenol lactone compounds as taught by Jones *et al.* with the GST-activated compound as taught by Kauvar *et al.*", Applicants submit that the rejection remains defective.

With regard to a rejection under 35 USC 103(a), MPEP 2143 states:
"To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991)."

First, there is no suggestion or motivation to combine the teachings of Jones *et al.* and Kauvar *et al.* because the haloenol lactones of Jones *et al.* are GST isoenzyme inhibitors, not GST-activated anticancer agents. Applicants do not dispute that Jones *et al.* describe their haloenol lactones as useful in combination cancer therapy as adjuncts to treatment with another anticancer agent, but the haloenol lactones themselves are not anticancer agents, they are GST isoenzyme inhibitors. Thus Jones *et al.* do not provide suggestion or motivation to replace the haloenol lactone GST isoenzyme inhibitors with an anticancer agent, still less the particular GST-activated anticancer agents of Kauvar *et al.* Nor do Kauvar *et al.* provide any suggestion or motivation to use their GST-activated anticancer agents in combination cancer therapy – they propose that the compounds may be used by themselves. Finally, while a person of ordinary skill in the art may be aware of combination cancer therapy, that knowledge is so general and the number of anticancer agents so great that it cannot be said that such general knowledge provides motivation for the combination of any particular pair of references such as Jones *et al.* and Kauvar *et al.* here.

The statement in the Office Action that "one would have been motivated to do so because as taught by Kauvar et al., in addition to the compounds being effective at treating cancer and/or drug resistance tumor cells, the GST activated compounds further provide a chemotherapeutic agent to a tumor cell while protecting the function of bone marrow" is not to the contrary. Nothing in Kauvar *et al.* suggests the use of its GST-activated anticancer compounds in combination cancer therapy or that a GST isoenzyme inhibitor would be useful in combination cancer therapy (since Kauvar *et al.* do not disclose GST isoenzyme inhibitors), and equally nothing in Jones *et al.* suggests that a GST-activated anticancer compound would be useful in combination cancer therapy because Jones *et al.* talk about GST isoenzyme inhibitors and not about GST-activated anticancer compounds, and give no reason to substitute a GST-activated anticancer compound for the haloenol lactone – since such a substitution would lose the GST isoenzyme inhibitory effect of the haloenol lactone and therefore the asserted combination cancer therapy benefit which is based (according to Jones *et al.*) on that GST isoenzyme inhibitory activity.

Second, there is no reasonable expectation of success in the proposed combination. This is true because, as explained above, there is no motivation for the combination. With no motivation, *a fortiori* there can be no expectation of success.

The statement in the Office Action that "one of ordinary skill in the art would have a reasonable expectation of success that by substituting the haloenol lactone compound for the GST-activated compound, one would achieve a method and/or pharmaceutical composition which protect the function of bone marrow" is not to the contrary. If the haloenol lactone compound of Jones *et al.* were substituted for the GST-activated compound of Kauvar *et al.*, one would be substituting a GST isoenzyme inhibitor for a GST-activated anticancer compound and would not meet the claims. And, if the GST-activated anticancer compound of Kauvar *et al.* were substituted for the haloenol lactone compound of Jones *et al.*, one would not have the GST isoenzyme inhibitory effect of the haloenol lactone and could not therefore have a reasonable expectation of the combination effect asserted by Jones *et al.*.

Since there is no teaching or suggestion to make the claimed combination nor any reasonable expectation of success in the prior art cited in the Office Action, no *prima facie* case of obviousness has been made out.

By not arguing the other aspects of the rejection (e.g. dosing), Applicants do not intend to be considered to agree with the Office Action's expression of those aspects – they are not being argued here because the issue of non-disclosure of a GST-activated anticancer compound by Jones *et al.*, and hence the non-combinability of Jones *et al.* and Kauvar *et al.* (the non-substitutability of the GST-activated anticancer compounds of Kauvar *et al.* for the GST isoenzyme inhibitors of Jones *et al.*), is dispositive of the propriety of the rejection.

Withdrawal of the rejection of claims 3-9, 20, and 23 is respectfully requested.

Applicants respectfully submit that all pending rejections have been addressed and that the present application is now in condition for allowance. Favorable reconsideration and allowance of the pending claims is respectfully requested. If the Examiner believes a telephone

conversation would help advance prosecution of the present application, the Examiner is cordially invited to contact the undersigned at the number below.

Respectfully submitted,

Date 30 May 2006

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